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## **Editorial: Special Issue on "Toxins: New targets and new functions".**

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Editorial

**22nd Meeting of the French Society of Toxinology (SFET)  
Special Issue on "Toxins: New Targets and New Functions"**

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The 22<sup>nd</sup> Meeting of the French Society of Toxinology (SFET) was held at the Pasteur Institute in Paris (December 10<sup>th</sup> - 11<sup>th</sup> December 2014) and had as main subject "Toxins: New Targets and New Functions". The meeting gathered more than 120 participants from Australia, Brazil, Europe, India, North and Central Africa, and the United States of America.

The first session was devoted to toxins acting on the nervous system. In this session **Emmanuel BOURINET** (Montpellier, France) reported that the T-type calcium channel Cav3.2 is a key regulator of sensory functions in touch/pain pathophysiology, with pharmacological relevance to relieve allodynia and hyperalgesia. Thus, the large potential of venom neurotoxins offers new venues for discovering subtype specific T-type channel blockers with high analgesic potential. **Eugene GRISHIN** (Moscow, Russia) showed that the natural peptides (Purotoxin-1 and -2), isolated from the spider *Alopecosa marikovskiyi*, possess selective inhibitory activity on purinergic P2X3 receptors. It seems likely that when the P2X3 receptors are desensitized, purotoxins bind to them and inhibit receptor activity. Purotoxin-1 demonstrated potent anti-nociceptive properties in animal models of inflammatory pain, since P2X3 receptors are expressed in mammalian sensory neurons and likely play a substantial role in pain perception.

Detailed information on inactive and active peptides, identified in the venom of the sea anemone *Urticina grebelnyi*, some of which selectively inhibited the ASIC3 channel, and significantly reversed inflammatory and acid-induced pain *in vivo*, were presented (see the original article by **OSMAKOV** *et al.* in this issue). Using site directed mutagenesis, the influence of individual amino acid substitution on the peptides was studied in order to determine the essential structural factor necessary for inhibiting ASIC3 activity. Also, short mutant peptides (22 amino acids), truncated at both N- and C-termini, were reported to exhibit a significant anti-inflammatory effect *in vivo*.

**Yara CURY** (Sao Paulo, Brazil) reviewed the antinociceptive effect of crotalphine, a peptide isolated from the South American rattlesnake *Crotalus durissus terrificus* venom, and the peripheral interactions between the opioid and cannabinoid systems in pain control.

**Grazyna FAURE** (Paris, France) presented new information on the actions of crotoxin, a potent  $\beta$ -neurotoxin from the venom of the rattlesnake *C. d. terrificus*, which exhibits PLA2 activity and neurotoxicity. Using surface plasmon resonance and other biochemical and biophysical techniques, two novel specific targets of the rattlesnake PLA2 were discovered including the cystic fibrosis transmembrane conductance regulator (CFTR) and the bacterial pentameric proton-gated ion channel (GLIC). Thus, GLIC was identified as a new protein target for PLA2 and PLA2 as a new ligand/regulator of GLIC proton-gated ion channel activity (see the original article by **OSTROWSKI** *et al.* in this issue). In addition, it was shown that the PLA2-GLIC interaction involves the extracellular domain of GLIC.

**Christian LEGROS** (Angers, France) reported the suitability of novel voltage-sensor probes to challenge the discovery of new inhibitors and modulators of voltage-gated sodium channels.

**Killian L'HERONDELLE** (Brest, France) reported a large release of substance-P and Calcitonin Gene-Related Peptide (CGRP) in a co-culture of human keratinocytes and rat dorsal root ganglia neurons exposed to Pacific-Ciguatoxin-2. These two neuropeptides have been shown to mediate or facilitate pruritus. Interestingly, the release of neuropeptides induced by P-CTX-2 involves TTX-resistant voltage-gated sodium channels. Up to now, ciguatera fish poisoning-associated pruritus has never been the subject of any study. This work provides an original way to better understand the pathophysiology of itch, and, at the same time, to identify potential targets for treating the sensory disorders of ciguatera (see the original article by **LE GARREC** *et al.* in this issue). A relevant novel model of motor nerve terminal degeneration followed by regeneration through the use of animal presynaptic neurotoxins from elapid snake ( $\beta$ -bungarotoxin) or from the black widow spider ( $\alpha$ -latrotoxin) was presented by **Cesare MONTECUCCO** (Padova, Italy).

The second session was mostly devoted to bacterial toxins and was presented by well-known scientists in their field. Many bacterial toxins are active intracellularly through enzymatic modification of intracellular target(s). Bacterial toxins use various enzymatic activities to induce their cytotoxic effects, and many of them have already been characterized and novel mechanisms and activities of bacterial toxins have been presented during the meeting. Indeed, a novel toxin called PaTox produced by the entomopathogenic bacterium *Photorhabdus asymbiotica* was identified by **Klaus AKTORIES** and co-workers (Freiburg, Germany). Their elegant work shows that PaTox exhibits a double enzymatic activity, inactivation of Rho-GTPases by a tyrosine glucosylation and activation of heterotrimeric G proteins ( $G_{\alpha q/11}$ ,  $G_{\alpha i}$ ) by deamidation of the essential glutamine in the GTP hydrolysis site resulting in alteration of the actin cytoskeleton (see the review article by **JANK** *et al.* in this issue).

*Pseudomonas aeruginosa* produces various toxins and virulence factors. Among them, ExoY is a type III secreted virulence factor which accumulates cyclic nucleotides (cAMP, cGMP, cUMP) inside the cells and promotes hyperphosphorylation of tau leading to microtubule disruption. **Undine MECHOLD** (Paris, France) and co-workers have identified a cellular cofactor which is required for the intracellular activity of ExoY.

An original remodeling of the cytoskeleton by some clostridial and *Staphylococcus* toxins (C3, EDIN) consists in the formation of transcellular tunnel allowing the passage of pathogens and/or toxins and virulence factors through endothelial barrier and their dissemination in the organism. The molecular mechanisms of tunnel formation have been investigated by the team of **Emmanuel LEMICHEZ** (Nice-Sophia Antipolis, France).

Most of intracellularly active bacterial toxins interact with a protein target, but some toxins specifically modify cellular DNA. This is the case of colibactin, a polyketide non-ribosomal peptide produced by certain extra-intestinal pathogenic *E. coli* strains. Colibactin cleaves double strand DNA and induces cell cycle arrest, as reported by **Jean-Philippe NOUGAYREDE** (Toulouse, France).

Binary toxins are a particular class of bacterial toxins that consist of two components, a binding component which transports *via* pore-formation through the endosomal membrane the enzymatic component into the cytosol which is the intracellularly active component. The interaction of the Panton and Valentine leukocidine, a staphylococcal binary toxin, with cell

membrane and the subsequent intracellular signaling cascade were discussed by **Gaëlle ZIMMERMANN-MEISSE** (Strasbourg, France).

The transport of the enzymatic component of clostridial binary toxins (*C. botulinum* C2 toxin, *C. perfringens* iota toxin, *C. difficile* CDT) through the pore formed by the binding components was reported to require host cell chaperones, as presented by **Holger BARTH** (Ulm, Germany).

The adenylate cyclase (CyaA) of *Bordetella pertussis* has the ability to directly translocate the catalytic domain through the plasma membrane avoiding endocytosis process. The interaction of CyaA with cell membrane was detailed by **Alexandre CHENAL** (Paris, France).

ESAT-6 (6-kDa early secreted antigenic target) is an essential virulence factor of *Mycobacterium tuberculosis* endowed with pore-forming activity. The current understanding of the role of ESAT-6 in the pathogenesis mechanism were presented and discussed, since ESAT-6 has become a major therapeutic target against *M. tuberculosis* infection (see the review article by **PENG and SUN** in this issue).

An important aspect in the study of the mechanisms of action and intracellular trafficking of bacterial toxins is the development of efficient countermeasures. **Neetu GUPTA** (Gif sur Yvette, France) reported the screening of chemical compounds that allowed identifying potent inhibitors of the intracellular traffic of Shiga toxin and ricin, offering perspectives for novel therapeutic strategies.

Botulinum neurotoxins are divided into seven toxinotypes, and each toxinotype enters target neurons *via* specific receptors, but all the botulinum neurotoxin types require reduction of the disulfide bond between the light (catalytic) and heavy chains for the release of the catalytic chain into the cytosol. The thioredoxin reductase-thioredoxin protein disulfide reducing system has been shown to be highly expressed in synaptic vesicles of motor nerve terminals, as reported by **Domenico AZARNIA TEHRAN** (Padova, Italy). This system is also responsible for the reduction of the interchain disulfide bond of botulinum neurotoxin/A, /C and /E. Remarkably, specific inhibitors of this system prevented the intoxication of cultured neurons by botulinum neurotoxins in a dose-dependent manner, and are also very effective *in vivo*. Interestingly, the thioredoxin reductase inhibitor auranofin, which prevents the intracellular membrane transport of diphtheria toxin catalytic component from endosomes into the cytosol, protected human cells, suggesting that auranofin might be a lead compound for developing novel therapeutic strategies to prevent/treat diphtheria (see the original article by **SCHNELL et al.** in this issue).

The third and fourth sessions of the meeting were dedicated to venom and toxins acting on different systems (cardio-vascular, renal, immune systems). **Diane BRINKMAN** (Townsville, Australia) reported the effects of the venom from *Chironex fleckeri*, one of the most dangerous box jellyfish to humans, which inflicts stings that can produce cutaneous pain, inflammation and necrosis, transient hypertension followed by hypotension, cardiovascular collapse and cardiac arrest. Also, she discussed, in the context of human envenoming, the toxins most likely responsible for the potent cardiovascular effects in experimental animals.

Animal venoms can be seen as large natural libraries of biologically active molecules that are continuously refined by the evolution process, up to the point where every molecule is endowed with pharmacological properties that are highly valuable in the context of human use and drug development. The interest of venoms as source of active peptides for the discovery of new therapeutic molecules at SANOFI was discussed by **Patrick JIMONET** (Vitry sur Seine, France). Instead of relying on classical low-throughput bioassay-guided approach to identify innovative bioactive peptides, **Michel DEGUELDRE** (Liege, Belgium) proposed a new paradigm to have access to venom diversity. The strategy combined high-throughput transcriptomic, proteomic and bioinformatics cutting-edge technologies to generate reliable peptide sequences. The discovered peptides were synthesized to generate a synthetic library of bioactive peptides. This library was finally screened against preselected biologic receptors. All steps were designed to evolve in high-throughput mode ensuring the best rate of discovery, in little time.

**Nicolas GILLES** (Gif-sur-Yvette, France) presented convincing evidence of the activity of mambaquaretin, a toxin discovered in the green mamba venom, and its synthetic homologue, both of which displaying a high inhibitory affinity for the vasopressin V2 receptor. Administration of mambaquaretin to a mouse model of genetically transmitted polycystic kidney disease resulted in an important inhibition of cyst growth, becoming a promising drug candidate with an original mode of action.

Secreted phospholipases A2 (sPLA2s) are disulfide bonded low molecular mass (14-19 kDa)  $\text{Ca}^{2+}$ -dependent enzymes with a His-Asp catalytic dyad. These multifunctional enzymes, first discovered in snake and insect venoms, are very diverse in structure and usually exert digestive and toxic functions towards preys, but also display many pharmacological actions. Based on the structural diversity of venom sPLA2s, it was hypothesized that there might be a similar structural diversity of sPLA2s in mammals, which would not only exert functions as enzymes, but would also act as endogenous ligands of the above identified receptors with venom sPLA2s, bringing the general concept of sPLA2s acting as both enzymes and ligands. It is now also clear, as showed by **Gérard LAMBEAU** (Valbonne, France), that individual mammalian sPLA2s are involved in diverse physiological and physiopathological processes.

The isolation and characterization of the antiangiogenic activity of two novel sPLA2 proteins from the venom of the most dangerous scorpion in Iran (*Hemiscorpius lepturus*) were reported by **Imen JRIDI** (Tunis, Tunisia). These novels nontoxic sPLA2s, which inhibit angiogenesis *in vitro*, could be new tools to disrupt different steps of angiogenesis progression.

The bee venom phospholipase A2 has been used as a membrane-binding vector to anchor a soluble protein fused to its C-terminus to the cell surface. ZZ, a two-domain derivative of staphylococcal protein A capable of binding constant regions of antibodies, was fused to the C-terminus of the phospholipase or to a mutant devoid of enzymatic activity. The fusion proteins bound to the surface of cells could bind IgGs. Their fate was dependent on the cell type to which they bound (see the original article by **BABON** *et al.* in this issue).

**Naoual OUKKACHE** (Casablanca, Morocco) presented detailed information on the proteomic characterization of two Moroccan scorpion venoms from *Androctonus mauretanicus* and *Buthus occitanus*. In addition, the ability of polyvalent antivenom to

prevent or reduce venom-induced mortality of mice, myotoxicity and neurotoxicity was reported.

The dynamic relationship between cellular and vascular events occurring in the microcirculation following *Loxosceles* envenomation was investigated in a murine model of loxoscelism. Remarkably, systemic administration of venoms from *Loxosceles intermedia* and *Loxosceles laeta* males and females revealed that microcirculation alterations were more intense in animals injected with female spider venoms. This correlated with a higher increase in the tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) and nitric oxide (NO) by the female venoms, compared with male venoms (see the original article by de **OLIVEIRA-LIMA** *et al.* in this issue).

Viper venoms contain complex mixtures of enzymatic and non-enzymatic proteins/peptides that have evolved with unique capabilities to affect a large number of physiological systems. Severe hematological and hemostasis alterations were reported to be initiated during the early stages, 3 and 6 hours after experimental administration of *Cerastes cerastes* and *Macrovipera mauritanica* venoms (see the original article of **FAHMI** *et al.* in this issue).

Venoms of the Sicariidae spider family are known to contain phospholipase D enzyme toxins that cleave phospholipid substrates and may cause necrosis, and even death, in humans. The chemistry and functional diversity of spider phospholipase D toxins was addressed by **Daniel LAJOIE** (Tucson, USA).

Crotamine is a small cationic peptide of 42 amino acid residues originally found in the venom of the South American rattlesnake *Crotalus durissus terrificus*. Consistent with the ability of crotamine to target acidic vesicles, an accumulation of the peptide was found in the lysosomes of the nematode *Caenorhabditis elegans*, used as host model. The anthelmintic activity of crotamine is due to its uptake by the worms and accumulation in their acidic compartments. The leakage of acidic endosomal/lysosomal vesicles is expected to ultimately underlie cell death (see the original article by **DAL MAS** *et al.* in this issue).

We warmly thank all those who made the 22<sup>nd</sup> meeting achievable, and we particularly acknowledge the important contribution of Professor Alan Harvey, Editor-in-chief of Toxicon, who made the publication of this proceedings possible as a Special Issue focused on “Toxins: New Targets and New Functions”. This Special Issue gathers 10 original peer reviewed original articles and reviews, and 48 abstracts, all reflecting those works and data presented during the SFET meeting. We hope that this Special Issue of Toxicon will be attractive and comprehensive source of information for students, researchers, and toxinologists.

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